

## **REMARKS**

### **Status of Claims**

Claims 20, 25, 29, and 31 have been amended with this response. Claims 1-19 and 22 were withdrawn from consideration by the Examiner as being drawn to a nonelected invention. Accordingly, claims 20, 21, and 23-32 are under consideration.

Support for the amendment to claim 20 can be found in the specification, for example at paragraph 0053. Support for the amendment to claim 31 can be found, for example, in paragraphs 0020-0021. The subject matter of amended claim 29 was encompassed by the previous wording of claim 25. Accordingly, no new matter is added with these amendments.

### **Argument**

#### **I. Rejection of claims 25 and 26 under 35 U.S.C. §102(b) over Bayes-Genis**

The Examiner has rejected claims 25 and 26 under 35 U.S.C. §102(b) for lack of novelty over Bayes-Genis et al. (*New England Journal of Medicine* 345(14): 1022-1029 (2001)). In particular, the Examiner asserts that "Bayes-Genis et al. disclose methods of measuring PAPP-A in acute coronary syndromes." Action at page 3.

In order to expedite prosecution, and without conceding in the correctness of the Examiner's rejection, Applicants have amended claim 25 to remove reference to PAPP-A. Thus, claim 25 now recites "(b) determining the concentration of PIGF." Bayes-Genis does not disclose measuring the concentration of PIGF in order to determine the prognosis of acute cardiovascular disease. Rather, Bayes-Genis only discloses the use

of PAPP-A to diagnose unstable angina and acute myocardial infarction. See Bayes-Genis at pages 1026-27.

In light of the amendment described above, claim 25 is not anticipated by Bayes-Genis. As claim 26 depends from claim 25, it is not anticipated either. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) of claims 25 and 26.

**II. Rejection of claims 20, 21, 23, and 24 under 35 U.S.C. §103 over Schönbeck in view of Corsini**

The Examiner has rejected claims 20, 21, 23, and 24 under 35 U.S.C. §103 over Schönbeck et al. (*Circulation* 104: 2266-2268 (2001)) in view of Corsini et al. (*Pharmacology & Therapeutics* 84: 413-428 (1999)). The Examiner previously rejected these claims over the same references. In the prior Office Action, the Examiner noted that Schönbeck disclosed methods of measuring soluble CD40L in patients with unstable angina. The Examiner then asserted that Schönbeck differed from the claimed invention only in failing to disclose the administration of statins as a therapeutic vascular agent to a patient, that Corsini taught the administration of statins to a patient, and therefore it would have been obvious to treat the detected vascular patients of Schönbeck with the statin drugs of Corsini.

In a previous response, Applicants argued that Schönbeck did not teach using sCD40L to monitor therapy, as required in claim 20. In particular, Applicants argued that monitoring of therapy related to controlling and/or adjusting the therapeutic treatment of an individual based on the measured concentration of at least one of the markers listed in claim 20. Neither Schönbeck nor Corsini taught or suggested the

usefulness of measuring serum levels of sCD40L to monitor therapy in that way. In response, the Examiner now asserts that a limitation requiring "monitoring of therapy with regard to the adjustment of treatment . . . [was] not recited in the claims." Action at page 4.

In response, Applicants have amended claim 20. In particular, claim 20 has been amended to state in subsection (e): "monitoring the therapy of an acute cardiovascular disease to detect an improvement or lack thereof in a pathophysiological condition, as indicated by a change in the concentration of the at least one inflammatory marker," while a subsection (f) has been added, stating: "adjusting the therapy of an acute cardiovascular disease, if necessary, in light of the improvement or lack thereof detected in (e)." Applicants submit that claim 20 now recites a method for "monitoring of therapy with regard to the adjustment of treatment," as suggested by the Examiner. Action at page 4. Subsection (e) allows for the detection of an effective or ineffective cardiovascular therapy, as measured by a change in the concentration of the at least one inflammatory marker being measured. Subsection (f) allows for appropriate action to adjust the cardiovascular therapy as necessary, or to maintain the same therapy, in light of the monitoring performed in step (e). Furthermore, as previously argued by Applicants, neither Schönbeck nor Corsini teaches controlling and/or adjusting the therapeutic treatment for an individual based on the measured concentration of at least one of the markers listed in claim 20, as recited in the presently amended claim.

In light of the amendment described above, claim 20 is not obvious over Schönbeck in view of Corsini. And as claims 21, 23, and 24 depend from claim 20, they

are not obvious either. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103 of claims 20, 21, 23, and 24.

**III. Rejection of claims 27 and 28 under 35 U.S.C. §103 over Maglione in view of Roger**

The Examiner has also rejected claims 27 and 28 under 35 U.S.C. §103 over Maglione et al. (*Il Farmaco* 55: 165-167 (2000)) in view of Roger et al. (*Journal of the American College of Cardiology* 34(1): 155-162 (1999)). In particular, the Examiner asserts that Maglione discloses "the measurement of PIGF-1 and VEGF in the measurement of various disorders including ischemic myocardium and infarct size." Action at page 5. The Examiner notes that Maglione does not specifically teach the detection of BNP, but the Examiner cites Roger for the proposition that "BNP is elevated in patients with heart failure, and serves as a sensitive and specific serologic marker for left ventricle dysfunction." *Id.* As such, the Examiner concludes that "[o]ne of ordinary skill in the art would have evaluated BNP in order to monitor blood flow as it relates to brain/cerebral disorders." *Id.*

In response, Applicants respectfully note that claims 27 and 28 relate to methods of diagnosing acute *cardiovascular* disease, not brain/cerebral disorders. Additionally, Applicants respectfully point out that while claim 27 *optionally* includes the measurement of BNP along with other markers of acute cardiovascular disease, the measurement of these additional markers is not required by claim 27.

Maglione discloses the synthesis and therapeutic use of recombinant human PIGF in animal models of myocardial ischemia and infarction. See Maglione, abstract. The reference concludes that PIGF could be used therapeutically to reduce the severity of acute myocardial infarction, based on the results obtained in animal models. See

Maglione at page 167 ("Discussion"). As such, Maglione does not disclose or provide motivation to use PIGF *diagnostically* by measuring PIGF levels in a biological sample obtained from a patient and correlating an abnormal concentration with a diagnosis of acute cardiovascular disease. Further, the mere fact that Maglione proposes treating acute myocardial infarction using PIGF does not necessarily indicate to one of skill that there is a correlation between the concentration of PIGF in a patient sample and a diagnosis of acute cardiovascular disease. Therapeutic targets are not necessarily also diagnostic indicators. Thus, one of skill would not conclude from Maglione's limited animal testing on the therapeutic uses of PIGF that a patient could be diagnosed with acute cardiovascular disease by measuring the PIGF concentration in a biological sample.

Further, Roger does not cure the deficiency of Maglione. Roger discloses the therapeutic use of nesiritide (human b-type natriuretic peptide) to treat decompensated heart failure and is silent on the measurement of PIGF to diagnose acute cardiovascular disease. Indeed, the entire purpose Roger was to evaluate the hemodynamic effects of three different doses of nesiritide when administered to symptomatic heart failure patients. See Roger, abstract and page 160. As such, Roger does not cure the deficiency of Maglione regarding the diagnosis of acute cardiovascular disease by measuring the PIGF concentration in a biological sample.

As such, claim 27 is not obvious over Maglione in view of Roger. And as claim 28 depends from claim 27, it is not obvious either. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103 of claims 27 and 28.

**IV. Rejection of claims 29-32 under 35 U.S.C. §103 over Schönbeck in view of Roger**

Finally, the Examiner has rejected claims 29-32 under 35 U.S.C. §103 over Schönbeck in view of Roger. In particular, the Examiner acknowledges that "Schönbeck et al. . . . differs from the instant invention in not specifically teaching the detection of BNP." Action at page 6. However, the Examiner asserts that "Roger et al. disclose methods [of] measuring BNP and its effects on hemodynamics. BNP is elevated in patients with heart failure, and serves as a sensitive and specific serologic marker for left ventricle dysfunction." *Id.* Thus, the Examiner concludes that it would have been obvious to combine Schönbeck with Roger to measure sCD40L and BNP, since "[t]he use of two known cerebral markers in combination to evaluate cerebral injury is obvious because expected beneficial results are evidence of obviousness." *Id.* at page 7.

In reply, Applicants respectfully note that claims 29-32 relate to methods of diagnosing and determining the prognosis of acute *cardiovascular* disease, not brain/cerebral disorders. Applicants also note that the focus of Roger is on the therapeutic use of nesiritide (human b-type natriuretic peptide) to treat decompensated heart failure, not on its diagnostic or prognostic uses. Indeed, the entire purpose of Roger was to evaluate the hemodynamic effects of three different doses of nesiritide when administered to symptomatic heart failure patients. See Roger, abstract and page 160. While Roger does briefly mention the use of endogenous hBNP as a serologic marker for left ventricular dysfunction in patients with heart failure, the main focus of the reference is on the therapeutic use of BNP. See Roger at page 155 (top of second column) and page 156 (top of first column). The mere passing reference in Roger to

measuring BNP is not sufficient to suggest to one of skill that measurement of BNP could be combined with measurement of at least one of sCD40L and PAPP-A in order to diagnose or determine the prognosis of acute cardiovascular disease. Therefore, Roger does not provide sufficient guidance for one of skill to expect success in diagnosing or determining the prognosis of acute cardiovascular disease by combining measurement of at least one of sCD40L and PAPP-A with the measurement of at least one additional marker such as BNP.

Furthermore, the use of BNP to treat heart failure is not even sufficient to indicate to one of skill that there is a correlation between a diagnosis of acute cardiovascular disease and the measured concentration of BNP, either alone or in combination with the at least one of sCD40L and PAPP-A. Therapeutic targets are not necessarily also diagnostic indicators. As such, one of skill would not have combined the teachings of Roger with those of Schönbeck (regarding measurement of sCD40L) to arrive at the claimed methods.

As such, claims 29 and 31 are not obvious over Schönbeck in view of Roger. And as claims 30 and 32 depend from claims 29 and 31, respectively, they are not obvious either. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103 of claims 29-32.

### **Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge  
any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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